Management of patients with diffuse intrinsic pontine glioma in Australia and New Zealand: Australian and New Zealand Children's Haematology/Oncology Group position statement

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Abstract

Introduction: The main mission of the Australian and New Zealand Children's Haematology and Oncology Group (ANZCHOG) is to develop and facilitate local access to the world's leading evidence-based clinical trials for all paediatric cancers, including brain tumours, as soon as practically possible. Diffuse intrinsic pontine gliomas (DIPGs) — a subset of a larger group of tumours now termed diffuse midline glioma, H3K27-altered (DMG) — are paediatric brain cancers with less than 10% survival at two years. In the absence of any proven curative therapies, significant recent advancements have been made in pre-clinical and clinical research, leading many to seek integration of novel therapies early into standard practice. Despite these innovative therapeutic approaches, DIPG remains an incurable disease for which novel surgical, imaging, diagnostic, radiation and systemic therapy approaches are needed.

Main recommendations:

- All patients with DIPG should be discussed in multidisciplinary neuro-oncology meetings (including pathologists, neuroradiologists, radiation oncologists, neurosurgeons, medical oncologists) at diagnosis and at relapse or progression.
- Radiation therapy to the involved field remains the local and international standard of care treatment.
- Proton therapy does not yield a superior survival outcome compared with photon therapy and patients should undergo radiation therapy with the available modality (photon or proton) at their treatment centre.
- Patients may receive concurrent chemotherapy or radiation-sensitising agents as part of a clinical trial.
- Biopsy should be offered to facilitate consideration of experimental therapies and eligibility for clinical trial participation.
- After radiation therapy, each patient should be managed individually with either observation or considered for enrolment on a clinical trial, if eligible, after full discussion with the family.
- Re-irradiation can be considered for progressive disease.

Changes in management as a result of the guideline: Every child diagnosed with DIPG should be offered enrolment on a clinical trial where available. Access to investigational drugs without biological rationale outside the clinical trial setting is not supported. In case of potentially actionable target identification with molecular profiling and absence of a suitable clinical trial, rational targeted therapies can be considered through compassionate access programs.

Diffuse intrinsic pontine glioma (DIPG) is a high grade glioma of the pons, predominantly occurring in children. It is one of the most aggressive paediatric cancers and remains essentially incurable.[1] In recent years, it has been grouped under the term "diffuse midline glioma, H3K27-altered" (DMG) to incorporate other aggressive high grade gliomas which also arise in the midline of the central nervous system and also carry the 3.3/3.1 H3K27 alterations or overexpression of the enhancer of zeste homolog inhibitory protein (EZHIP). Thus, DMGs also include tumours that arise in other midline structures, including the thalamus and the spinal cord.[2] Although many of the principles in this position statement apply to all DMGs, we are specifically referring to DIPGs, which form the majority of DMG cases.

About 20–30 children in Australia and New Zealand are diagnosed with DIPG each year. The median survival for children with DIPG is less than one year from diagnosis,[3] with more than 90% dying within two years of diagnosis.[4-6] Radiation therapy remains the current standard of care. Conventional radiation therapy in a dose of 54–60 Gy over a six-week period is commonly used in the treatment of DIPG.[5] Temporary improvement or stabilisation of symptoms is seen in 70% of patients, but, essentially, all patients ultimately develop progressive disease, with a mean progression-free survival of six to eight months.[4] A multitude of prior studies have not demonstrated a role for chemotherapy[7-9] or radiation-sensitising agents in the treatment of DIPG,[10-12] leaving radiation therapy as a palliative standard of care therapeutic modality.

Historically, given the risks associated with a pontine tumour biopsy, combined with the lack of a clear therapeutic benefit from obtaining a biopsy, as well as characteristic clinical and radiological findings, magnetic resonance imaging (MRI) scans became the diagnostic standard of care for DIPG.[13] More recently, there has been a renewed interest in the procurement of biopsy and autopsy samples in patients with DIPG.[14] Availability of tumour samples has provided invaluable insights into the understanding of DIPG biology[8,15] and potential novel therapeutic strategies. Without tissue to investigate, DIPG will remain incurable and palliative radiation therapy will continue to be the only recommended treatment outside of a clinical trial with evidence of benefit. Biomolecular studies on tumour biopsies and autopsies received over the past decade have provided the rationale for investigating molecularly targeted agents (eg, everolimus, sunitinib, paxalisib), epigenetic modifying agents (eg, panobinostat, vorinostat, CBL0137), and immunotherapy including immune checkpoint inhibitors (eg,

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nivolumab, ipilimumab) and chimeric antigen receptor (CAR) T cells.[16-19] More recently, these data have led to the investigation of newer agents given as monotherapy or in combination, such as ACT001 (a novel plasminogen activator inhibitor-1 [PAI-1] inhibitor; www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=376262) difluoromethylornithine (DFMO) and AMXT1501 (a polyamine transport inhibitor, https://clinicaltrials.gov/study/NCT05500508), avapritinib (a selective platelet-derived growth factor receptor alpha [PDGFRA]/KIT inhibitor, https://classic.clinicaltrials.gov/ct2/show/NCT04773782) and ONC201 combined with paxalisib in the international clinical trial PNOC022 (https://clinicaltrials.gov/study/NCT05009992).[20]

In recognition of the devastating disease course experienced by all patients and their families, as a medical and scientific community, we are dedicated to improving their outcomes. We holistically value our patients and hold their best interests as paramount. As a specialist paediatric neuro-oncology group in Australia and New Zealand, we strive to make advances in the management of patients with DIPG in keeping with the international community and hope to deliver curative therapies in the future. The consensus method was used to bring together this group of experts and build on their individual experiences and opinions with the objectives of:

- reviewing and presenting a critical analysis of the current evidence for DIPG;
- describing current best practice recommendations for the diagnosis and treatment for patients with DIPG; and
- providing a reference guideline for patients, carers and professionals working in the field of DIPG in Australia and New Zealand.

To our knowledge, there is no other equivalent national position statement elsewhere globally; therefore, this statement can be useful as a reference document for other national collaborative groups.

Methods

Selection of the working group members

ANZCHOG Central Nervous System (CNS) Tumours Group is an expert body on childhood brain tumours under the umbrella of ANZCHOG. It strives for excellence in clinical care, research, professional education and purposeful stakeholder advocacy. The group comprises 20 paediatric neuro-oncologists from 11 children's cancer centres and six paediatric brain tumour researchers from Australia and New Zealand.

All members of the ANZCHOG CNS Tumours Group were part of the working group tasked with the development of this position statement. By including the entire group in the process, there is a higher likelihood of development of a robust and credible position statement. In addition, a paediatric radiation oncologist and two consumer representatives reviewed the position statement and provided their feedback.

To comply with the Journal's authorship guidelines, ten members from the group were selected as the authors based on their contribution to the position statement and positions as lead clinicians at each centre. Participating authors declared all competing interests.

Assessing consensus

The RAND/UCLA Appropriateness Method (RAM) was used to reach consensus.[21] The RAM panel method is an internationally recognised technique using a panel of experts to inform the content of policies under development.

The scope and development process of the position statement was discussed at the group's meeting in Sydney on 30 July 2022. A systematic literature review until 1 March 2023 was undertaken by one author (SV). The PubMed search included the terms "diffuse intrinsic pontine glioma", "diffuse midline glioma H3K27M altered", "brainstem glioma" and "paediatric high-grade glioma". Systematic reviews, meta-analyses and clinical trial results were prioritised, and publications were limited to those written in English.

Four working group members (SV, MM, NM and JH) summarised the existing scientific evidence in a draft manuscript, which was distributed to the group members via email ahead of discussing in the group's meeting in Brisbane on 23 March 2023. Members of the group deliberated on relevant evidence from personal experience, knowledge and literature review.

The recommendations were accompanied by a Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system. The strength of recommendation was graded as "strong" or "weak" as guided by the quality of evidence ("high", "moderate", "low" or "very low").

All working group members reviewed and edited the manuscript through extensive email communication before and after this meeting. SV collated, processed and synthesised the responses and facilitated resolution of differing opinions by discussion within the group. Updated versions of the manuscript were redistributed among the working group via email. Consensus was reached with categorical rating (all members agreeing) for each diagnostic and therapeutic recommendation. The final version of the position statement was approved by all authors.

Recommendations

Diagnosis

The recommendations for the diagnosis are summarised in Box 1.

Imaging. A computed tomography (CT) scan alone, owing to its lower tissue resolution, is insufficient to make a diagnosis of DIPG, but it can still be used as a first line screening tool.[22] The choice of diagnostic imaging modality is magnetic resonance imaging (MRI) before and after the administration of a gadolinium-based contrast agent. The differential diagnoses for DIPG include pilocytic astrocytoma, embryonal tumours, demyelinating disease and vascular disease, making MRI the best diagnostic

1 Recommendations for the diagnosis

- Magnetic resonance imaging is the diagnostic modality of choice (*Strong recommendation; high quality of evidence*).
- Biopsy should be offered to facilitate consideration of experimental therapies and eligibility for clinical trial participation (*Strong recommendation; moderate quality of evidence*).
- All patients with diffuse intrinsic pontine glioma should be discussed in multidisciplinary neuro-oncology meetings (including pathologists, radiation oncologists, neurosurgeons, and medical oncologists) at diagnosis and at relapse or progression (*Strong recommendation; high quality of evidence*).

study.[23] MRI can reliably distinguish the subtypes of brainstem glioma, including focal, dorsal exophytic, cervicomedullary and diffusely infiltrating brainstem tumours.[24] In addition, clinical trials participation mandates response assessment with MRI, making baseline MRI a necessity.[25] Patients with DIPG are treated at tertiary care paediatric centres where MRI scanning is readily available. On MRI, the lesions are expansile, typically hypointense on T1 weighted images and hyperintense on T2 weighted images.[26]

Other imaging modalities including, but not limited to, magnetic resonance spectroscopy with estimation of choline to N-acetylaspartate (Cho:NAA) ratios,[27] rapid diffusion MRI, thallium single-photon emission computed tomography (SPECT)[28] and 18-fluoride-fluoroethyl-tyrosine positron emission tomography ([^{18}F]FET-PET)[29] are experimental and currently not widely available. However, if available, these modalities may be useful and appropriate, particularly in difficult or unclear cases. Imaging features of DIPG are summarised in Box 2.[23,26,30]

Biopsy. If imaging findings are typical of DIPG, biopsy has not been necessary historically to confirm the diagnosis,[31,32] while biopsy has been routinely employed in tumours that originate outside the pons (ie, thalamus and spinal cord).[24] Recent studies have shown that biopsies of DIPG can be conducted safely using stereotactic-guided techniques employed by appropriately trained neurosurgeons.[33] The Second Consensus Conference on Paediatric Neurosurgery recommended biopsy in all patients with DIPG to ascertain biological characteristics to enhance understanding and targeting of treatment,[34] and should be considered in the context of a clinical trial (eg, ZERO Childhood Cancer Program [ZERO2], https://classic.clinicaltrials.gov/ct2/show/NCT05504772). Some recent trials, such as PNOC022), include mandatory biopsy requirements, with pre-biopsy treatment in some cohorts, to help determine the concentration of the drug in the tumour and, hence, derive correlative data to identify the prospective potential of these therapies.

Biopsy should also be considered for patients with a long duration of symptoms and atypical clinical and/or imaging findings. For example, up to one-quarter of adult brainstem gliomas have isocitrate dehydrogenase 1 (*IDH1*) mutations, mostly non-R132H variants,[35] and biopsy may help to identify these patients with improved prognosis and to guide precision therapy.

In keeping with ANZCHOG's mission of achieving excellence in research, we encourage biopsy where appropriate and feasible after having a thorough discussion with families and obtaining informed consent. Tumour samples can be used for identification of molecular aberrations for potential targeted therapies or clinical trial enrolment for that individual patient as well as advancement of research in the field of DIPG, such as by establishing novel patient-derived tumour cell lines or xenografts.[36] These tissues should be shared nationally and internationally with the DIPG research community with appropriate research ethics and governance in place. National initiatives to enhance sharing of tissue samples and sequencing results include active collaboration between members of the ANZCHOG Biobanking Network[37] as well as access requests within the ZERO Childhood Cancer Program. In Europe, the European Society for Paediatric Oncology (SIOPE) DIPG Network has established a virtual biobank of DIPG material linked with the DIPG Genomics Repository at Progenetix, which is a cancer genome database.[38] The International DIPG/DMG Registry is comprised of centres from the United States, Canada, Australia and New Zealand, has a pathology repository containing DIPG tumour tissue.[39] The Children's Brain Tumor Network (CBTN) is a multi-institutional international clinical research consortium facilitating the collection and rapid distribution of biospecimens and data via open science research platforms.[40] These are examples of successful alliances sharing DIPG tumour tissue leading to collaborative research projects.

2 Typical imaging features of diffuse intrinsic pontine glioma (DIPG)

- DIPG appears in isodense or hypodense on computed tomography images.
- Magnetic resonance imaging (MRI) demonstrates an expanded pons with encasement of basilar artery.
- Typically, > 50% of the ventral pons shows signal changes on the T2-weighted-fluid-attenuated inversion recovery (T2-FLAIR) MRI sequence.
- Lesions are hypo-intense on T1-weighted and hyperintense on T2-weighted MRI images, with ill-defined margins keeping in with the infiltrative nature of DIPG.
- There is no contrast enhancement on T1-weighted post contrast MRI images except for around foci of necrosis.
- Sagittal imaging classically shows a clear pontomedullary demarcation.

3 Recommendations for therapy

- The local and international standard of care treatment is involved field radiation therapy (*Strong recommendation; high quality of evidence*).
- Proton therapy does not yield a superior survival outcome compared with photon therapy and patients should undergo radiation therapy with the available modality (photon or proton) at their treatment centre (*Strong recommendation; moderate quality of evidence*).
- Patients may receive concurrent chemotherapy or radiation sensitising agents as part of a clinical trial (*Weak recommendation; weak quality of evidence*).
- After radiation therapy, each patient should be managed individually with either observation or considered for enrolment on a clinical trial, if eligible, after full discussion with the family (*Strong recommendation; high quality of evidence*).
- Re-irradiation can be considered for progressive disease (*Strong recommendation; moderate quality of evidence*).

Therapy

The recommendations for therapy are summarised in Box 3.

Radiation therapy. For many years, radiation therapy has been administered by using photons (ie, x-rays). Photon therapy is delivered as intensity-modulated or three-dimensional conformal radiation therapy using multiple x-ray beams to irradiate a tumour target but depositing radiation in normal tissues in the process.[41] Proton therapy involves particle radiotherapy depositing relatively constant energy up to the Bragg peak with a subsequent drop resulting from the depth dose distribution of particles. This therapy offers the advantage of protecting the surrounding healthy organs by reducing the radiation dose behind the Bragg peak.[42] Proton therapy does not yield a superior survival outcome compared with photon therapy and patients should undergo radiation therapy with the available modality (photon or proton) at their treatment centre.[43]

Radiation therapy is delivered to a total dose of between 54 Gy and 60 Gy over 30 daily fractions (Monday to Friday).[5,42] If patients are unwell or from remote locations, shortened courses of radiation of 39 Gy in 13 fractions or 45 Gy in 15 fractions can be considered.[44]

In the case of disease progression, re-irradiation can be considered for symptom control if disease progression occurs six months or more after initial radiation therapy.[45,46] This can be offered on its own or in the setting of a clinical trial such as ReRAD (https://classic.clinicaltrials.gov/ct2/show/NCT03126266). Radiation doses

will vary according to individual patient circumstances and local radiation oncologist recommendation. Within the ReRAD trial, the dose of radiation therapy is adjusted based on the duration between completion of initial radiation therapy and tumour progression. In the trial, if this period is six to 18 months, patients receive 30.6 Gy in 17 fractions, whereas if the progression is after 18 months, they receive 36 Gy in 20 fractions.

As recommended by the Brain Tumour Imaging Standardisation Steering Committee, an MRI scan should be performed four to six weeks after completion of radiation therapy as a new baseline for disease monitoring.[25]

Chemotherapy. Conventional chemotherapy provided concurrently with, or adjuvant to, radiation therapy does not currently have an established role in the management of DIPG.[5] The use of chemotherapy is considered investigational and should only be provided in the context of a clinical trial.

Surgery. Due to the tumour location in the pons, which controls essential physiological functions, including breathing and heart rate, and the potential for significant and permanent morbidities affecting quality of life, or death, there is no role for surgical excision in patients with DIPG.[47] We do not recommend surgical intervention apart from biopsy or, in some cases, insertion of a ventriculoperitoneal shunt or reservoir.[48]

Use of dexamethasone and bevacizumab. Dexamethasone is commonly used for symptomatic management by reducing oedema surrounding the tumour.[49] It is frequently associated with debilitating side effects, especially with prolonged use, including weight gain, increased appetite, behavioural and sleep disturbance, high blood pressure and elevated blood sugar levels. Dexamethasone should be weaned to the lowest tolerable dose during or after radiation therapy depending on the clinical condition of the child. The use of bevacizumab may be considered as a steroid-sparing agent or in the management of radiation necrosis.[50]

Access to newer therapies. The current lack of curative therapy for DIPG often results in a loss of hope from both the medical community and family members. With frequent input from well meaning friends and relatives, this often leads to active and desperate seeking of therapeutic alternatives.[51] Unfortunately, this can often result in unfounded beliefs in miracle cures[52] and seeking the use of new and novel medications, often at great personal cost to families, outside of the clinical trial settings.[53,54] Potential side effects are not captured in these non-trial settings and this information cannot be used in a meaningful way to help future patients. Our aim is to offer innovative, experimental trials to every child diagnosed with DIPG with a compassionate and caring attitude. ANZCHOG centres are involved in a broad array of research activities, establishing partnerships with international cooperative groups and sponsoring local research projects and clinical trials, where appropriate, and with approval from human research ethics committees. The ANZCHOG Children's Cancer Clinical Trials Repository (ACCCTR) provides a complete, up-to-date list of clinical trials conducted in children's cancer centres in Australia and New Zealand. The information provided should be used in conjunction with advice from health care professionals. Soon after diagnosis, the primary oncologists are encouraged to proactively discuss with families the availability of a suitable open clinical trial at their local centre and other centres nationally. ANZCHOG centres will work collaboratively as a network to provide access to clinical trials that may not be open at particular centres. However, with the more recent availability of molecular tumour profiling, such as through Precision Medicine for Children with Cancer (PRISM; https://clinicaltrials.gov/search?term=NCT03336931) and ZERO2 diagnostic trials and national molecular oncology tumour boards, there may be actionable targets identified and the opportunity to obtain targeted therapies through compassionate access programs. Otherwise, access to investigational drugs outside the clinical trial setting is generally not advisable and is not supported by the ANZCHOG CNS Tumours Group.

Referral for second opinion

ANZCHOG clinicians work closely with their national and international collaborators to identify better therapies for all children with brain tumours, including DIPG, and will facilitate second opinions when requested. Involving the primary oncologist in the referral process helps to facilitate accurate information and open communication in the best interests of patients and their families.

Autopsy

There is evidence that parents experience benefit after donating their child's autopsy sample for research. Parents have expressed that this has helped with their grieving process knowing that the donation has the potential to improve the biological understanding of DIPG and to assist other children in the future.[55,56] Autopsy tumour sampling should be considered for all families and offered where logistically feasible. Discussions on autopsy donation are encouraged early in the treatment course but the decision to donate remains in the hands of the child's family and can be revisited by the parents or guardians at any stage before the autopsy.[57]

Conclusions

DIPG remains a uniformly fatal disease. Due to the courage of families over recent times and their willingness to donate the necessary tissues of their child's tumour, as well as to fund critical medical research, new clinical trials are exploring the utility of novel therapeutic strategies and innovative cellular-based therapies for the treatment based on the unique biology of DIPG. While we as a clinical, research and consumer community await outcome data from these national and international clinical trials, our main priority is the care and wellbeing of our patients and their families. Australia and New Zealand CNS tumour clinicians and researchers in partnership with ANZCHOG are working to expedite new and improved treatments to increase survival of our patients and remain focused on opening the best evidence-based national and international clinical trials across all major paediatric hospitals around Australia and New Zealand as quickly as possible.

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